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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/814,873	12/24/91	WAYNER	CYTE-1-6162

GAMBEL, E EXAMINER

18M2/0615

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ART UNIT	PAPER NUMBER
1806	16

DATE MAILED: 06/15/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 3/23/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-5, 32-36 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims 6-31, 37-63 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-5, 32-36 are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 1-63 are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Applicant's election without traverse of Group I in Paper No. 13 is acknowledged.

Claims 1-5 and 32-36 are pending.
Claims 6-31 and 37-63 are canceled without traverse.

16. If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application.

It is noted that serial number 07/402,389 is stated in the oath and that specification on page 1 should be amended to disclose said application and the relationship between said application and the instant application.

17. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

18. The disclosure is objected to because of the following informalities: page 17, line 7 - "bacille" should be "Bacille"; page 18, line 23 - "e" should be "be"; page 46, line 5 - "Epsten" should be "Epstein"; and page 52, line 7 - "intestingly" should be "interestingly"; .

Appropriate corrections are required.

19. The disclosure is objected to as failing to comply with 37 CFR 1.821(d). The sequence I.D. number should be disclosed with each sequence listing. The examiner has noted the following: page 22, lines 3, 6 and 31; page 25, line 3, page 50, line 32; page 52, lines 7 and 10; page 56, line 17; page 57, line 8, 2, 32 and 33; page 59, line 33, page 65, line 3; page 68, lines 13, 14, 25, 30 and 33; page 69, lines 7 and 10, page 71, lines 19 and 26 and page 72, line 11. Applicant should review the dislosure carefully for compliance with sequence rules.

Appropriate corrections are required.

For information only, applicant is reminded that the sequence I.D. number should be recited with each sequence listing in the claims as well. Such claims have been canceled in the instant application.

20. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

21. Claims 1-5 and 32-36 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. The specification fails to establish the utility of the claimed $\alpha 4\beta 1$-specific antibodies as therapeutic agents to block lymphocyte adherence and migration in human patients. Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. It is well known in the art that the jump from such in vitro assays and in vivo animal studies to in vivo human efficacy is a major barrier indeed. This is succinctly summed up by the recent meeting report by Harris et al. which states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses. (page 42, column 3). Waldmann teaches that effective therapy using monoclonal antibodies in the therapy of human diseases due to the pharmacokinetic properties of rodent antibodies in human and human anti-mouse antibody responses. Waldmann also indicates that hopes for antibody-based treatment methods engendered by in vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Even chimeric or humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies contain unique amino acid sequences. Therefore, it does not appear that the asserted utility of the claimed method for treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01 (p).

22. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

A) Applicants have not disclosed how to use $\alpha 4\beta 1$-specific antibodies therapeutically in humans. There is insufficient written description of the invention with respect to the in vivo operability of $\alpha 4\beta 1$-specific antibodies to use applicant's invention for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see paragraph 20). Although $\alpha 4\beta 1$-specific antibodies have been able to block lymphocyte adhesion to endothelial cells in vitro to some degree (see Table IX), no examples have appeared in the application of $\alpha 4\beta 1$-specific immunotherapy in vivo. It is not clear from the specification whether $\alpha 4\beta 1$-specific antibodies can inhibit lymphocyte adherence or migration in humans and to what degree. Therefore, it does not appear that the asserted operability of the claimed method and compositions for inhibiting lymphocyte adherence and migration in vivo in humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

B) It is unclear from the specification whether any $\alpha 4\beta 1$-specific antibody can inhibit lymphocyte adhesion and migration in vivo. Applicant has exemplified some inhibition of lymphocyte adhesion to activated endothelial cells with the P4C2 and P4C10 monoclonal antibodies only (see Table IX). Even in this showing, inhibition was not complete. Also, applicant has indicated that $\beta 1$-specific antibodies such as 8A2 can stimulate adherence (see page 71, paragraph 2). There is no evidence relating to the inhibition by any $\alpha 4\beta 1$-specific antibody to practice all of the inhibitory effects on adhesion and migration embraced by the claims. The disclosure is not enabled for inhibition using any $\alpha 4\beta 1$-specific antibody, all of which are embraced by the claims.

Compositions comprising any $\alpha 4\beta 1$-specific antibody do not necessarily correlate with their ability to inhibit lymphocyte adhesion and migration. The specification has not provided sufficient directon or guidance to one of skill in the art to properly select or administer $\alpha 4\beta 1$-specific antibody that are required to practice the broadly claimed methods. It appears that undue experimentation would be required of one skilled in the art to practice the broadly claimed methods using the teaching of the specification alone.

C) It is apparent that the P4C2, P4C10, P4G9 and P3E3 are required to practice the claimed invention as claimed in the specification and cited in the claims. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of P4C2, P4C10, P4G9 and P3E3 hybridomas. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining P4C2, P4C10, P4G9 and P3E3 and they do not appear to be readily available materials. Deposit of the P4C2, P4C10, P4G9 and P3E3 hybridomas would satisfy the enablement requirements of 35 U.S.C. 112.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability ot the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

c) the deposit will be maintained for a term of at least thirty years and at least five years after the most recent request for the furnishing of a sample of the deposited material;

d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

24. Claims 1-5 and 32-36 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see paragraphs 21-22).

25. Claims 1-5 and 32-36 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 and 32-36 are indefinite in the recitation of "a fragment or derivative thereof" because the characteristics of the "fragments" or "derivatives" defined by claims 1-5 and 32-36 are not known. These "fragments" or "derivatives" could be any peptide that binds $\alpha 4\beta 1$. No direction or guidance is provided to assist one skilled in the art in the selection of such "fragments" or "derivatives" nor is there evidence provided that such "fragments" or "derivatives" would be therapeutically effective. It appears that undue experimentation would be required of one skilled in the art to practice the method of claims 1-5 and 32-36 using the teaching of the specification alone. It is suggested that "antigen-binding fragments" would be a clearer term.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

26. Claim 32 is rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is indefinite in the recitation of "via an extracellular matrix receptor" because the characteristics of the "extracellular matrix receptor" defined by claim 32 is not known. These "extracellular matrix receptors" could be any receptor associated with the extracellular matrix. No direction or guidance is provided to assist one skilled in the art in the selection of the appropriate "extracellular matrix receptor" nor is there evidence provided that any "extracellular matrix receptor" would be therapeutically effective as a target for inhibiting lymphocyte migration. It appears that undue experimentation would be required of one skilled in the art to practice the method of claim 32 using the teaching of the specification alone. It is suggested that the $\alpha 4\beta 1$ receptor of claim 33 be brought into the claim language.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

27. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

28. Claims 1-4 and 32-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Shimizu et al. in view of Carlos et al. and Wayner et al. Claims 1-4 and 32-35 are drawn to inhibiting lymphocyte adherence and migration to endothelial cells. Shimizu et al. teach the role of adhesion molecules including VLA-4 $\alpha 4\beta 1$ and β chains in T cell recognition (see entire document). Shimizu et al. teach the inhibition of $\alpha 4\beta 1$ and β chains $\alpha 4\beta 1$ and β chain-specific antibodies <u>in vitro</u> see pages 116-118 and Figure 2). Shimizu et al. teach that T cell VLA-4 in both binding and proliferation interacts with the CD-1 sequence found in the IIICS

region of the fibronectin molecule and cites Wayner et al. (see page 125). Shimizu et al. teaches that the higher expression of VLA-4, VLA-5 and VLA-6 on the memory subset of T cells is correlated with increased bvidning capacity of these cells and contributes to their migration (see page 128, paragraph 1 and page 133, paragraph 1). Shimizu et al. teach that the physiologic function of these adhesion interactions would be associated with the interaction of T cells and endothelial cells, the selective binding of T cells to particular endothelial cells and the preferential migration of lymphocyte populations to inflammed tissue (see pages 132-137). Shimizu et al. also teach that the extracellular matrix impacts T cell activities both by direct interaction and by bridging (see page 135). Shimizu et al. differs from the instant invention by not teaching the therapeutic role of $\alpha 4\beta 1$ and β chain-specific antibodies per se. Carlos et al. reach the role adhesion molecules in leukocyte adherence to endothelium (see entire document). Carlos et al. teach the role of VLA-4 in leukocyte adherence including the inhibition of leukocyte adherence to activated endothelium cells by VLA-4-specific antibodies including P4C2 of the instant invention (see page 14). Carlos et al. review the exemplification of blocking leukocyte adherence and migration in vivo by anti-adhesion molecule specific antibodies including those specific for α and β chains (see pages 165-21, particularly Tables II and IV). Wayner et al. exemplify the identification and characterization of the T cell adhesion receptor for CS-1 domain in plasma fibronectin (see entire document) cited above in both Shimizu et al. and Carlos et al. Here, Wayner et al. teach the identification of inhibitory regions of adhesion molecules and the production of specific antibodies including P4C2 of the instant claims. Wayner et al. also teach the importance of the IIICS region of fibronectin during wound healing and inflammation in the specificity of T cells (see page 1330, column 1). Therefore, it was known at the time the invention was made that $\alpha 4\beta 1$ and β chain-specific interactions were important in lymphocyte adherence and migration and that these interactions were inhibitable by $\alpha 4\beta 1$ and β chain-specific antibodies both in vitro and in vivo. One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of inhibiting lymphocyte adhesion and migration by immunotherapy with $\alpha 4\beta 1$-specific antibodies as a therapeutic regimen in treating human inflammation. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

It is noted that rejections cited in paragraph 28 above and and paragraph 29 below are presented in the absence of fulfilling the requirement of priority of the instant application cited in paragraph 16 above.

29. Claims 5 and 36 are rejected under 35 U.S.C. § 103 as being unpatentable over Shimizu et al., Carlos et al., Wayner et al. as applied to claims 1-4 and 32-35 above and in further view of Carter et al. Claims 5 and 36 are drawn to inhibiting lymphocyte adherence and migration to endothelial cells by the P4C10-specific antibody. Shimizu et al., Carlos et al., Wayner et al. have been discussed supra in paragraph 27 above. Carter et al. exemplify the inhibition of cell adhesion by the particular β1-specific P4C10 antibody of the instant invention (see page 1397 and Figure 8). Carter et al. also teach the importance of the β1-specific as well as the CS-1 domain of fibronectin in cell adhesion (see page 1403, column 1). It would not have been expected that the β1-specific P4C10 cited in the claims would have differed from the β1-specific antibodies cited in Shimizu et al. and Carlos et al. cited above. Therefore, it was known at the time the invention was made that α4β1 and β chain-specific interactions were important in lymphocyte adherence and migration and that these interactions were inhibitable by α4β1 and β chain-specific antibodies both in vitro and in vivo. One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of inhibiting lymphocyte adhesion and migration by immunotherapy with α4β1-specific antibodies as a therapeutic regimen in treating human inflammation. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

30. Claims 1-4 and 32-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Hemler (Immunol. Today) in view of Stoolman (Cell) and Pitzalis et al. (Eur. J. Immunol.). Claims 1-4 and 32-35 are drawn to inhibiting lymphocyte adherence and migration to endothelial cells. Hemler reviews the structure of VLA antigens including the association of distinct α subunits with a common β subunit (see entire document). Hemler teaches that specific antibodies were made to distinguish between the VLA variants. Hemler teach that VLA-4 composed of $\alpha 4\beta 1$ is expressed on nearly all lymphocytes, monocytes and related cell lines. Hemler teach the importance of adhesion molecules for leukocyte adherence to vascular endothelium cells which precedes leukocyte emigration to extravascular tissue. Hemler does not teach the use of $\alpha 4\beta 1$ and β chain-specific antibodies to inhibit lymphocyte adherence per se. Stoolman also reviews the role of adhesion molecules in the recruitment and migration of lymphocytes into inflammatory lesions (see entire document). Stoolman teaches that a monoclonal antibody LPAM-1 effectively blocked lymphoid-endothelial cell binding and that this antibody specificity cross-reacted with anti-human VLA-4 (see page 907, column 2, paragraph 3). Stoolman teaches that blocking lymphocyte-endothelial interactions could be accomplished by anti-adhesion antibodies in vitro and in vivo (for example, see page 908, column 1, paragraph 1). Pitzalis et al. teach high levels of CD29, the $\beta 1$ subunit shared by VLA integrins, are characteristic of a subset of lymphooyctes enriched in chronic inflammatory sites (see entire documnet). Therefore, it was known at the time the invention was made that $\alpha 4\beta 1$ and β chain-expressing cells were involved at inflammatory sites and that anti-adhesion antibody treatment inhibited leukocyte-endothelial cell interactions in vitro and in vivo. One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of inhibiting lymphocyte adhesion and migration by immunotherapy with $\alpha 4\beta 1$-specific antibodies as a therapeutic regimen in treating human inflammation. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

31. No claim is allowed.

V. CHRISTINA CHAN
PRIMARY EXAMINER
GROUP 180

32. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
June 9, 1993

Y. CHRISTINA CHAN
PRIMARY EXAMINER
GROUP 180
Art Unit 1806